PATENT SPECIFICATION

1,123,317

NO DRAWINGS

1,123,3

Date of Application and filing Complete Specification: 19 Dec., 1966.
No. 56839/66.
Application made in United States of America (No. 516,120) on 23 Dec.,
Application made in United States of America (No. 562,117) on 1 July,
Complete Specification Published: 14 Aug., 1968.

Index at acceptance:—C2 C(1F1A2, 1F1B, 1F1D3, 1Q2, 1Q6C, 1Q7A, 1Q8A, 1Q9A, 1
1Q11J, 2A2, 2A6, 2A13, 2B30, 2B40D, 2B40G, 2B40H2, 2
2B40J3, 2B48C1, 2B48G3, 2B49C1, 2B49G3, 2B51C1, 2D3, 2R15,
3A13C6B, 3A13C10D, LG32Y, LG36Y, LG45Y, LG220, LG321, I
LG453, LG610, LP32Y, LP220, LP321, LP332, LP470, LP611, I
LP621, LP660, LP661, LW32Y, LW36Y, LW220, LW321, L
LW364, LW660, LW661); A5 B2S

Int. Cl.:—C 07 d 49/38

COMPLETE SPECIFICATION

Anthelmintic Compositions containing Benzimidazole Derivatives

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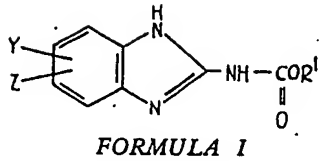
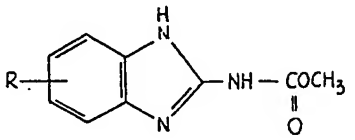
Page 5, line 7, *for* "formula" *read* "Formula"
Page 6, line 126, *for* "70" *read* "10"

THE PATENT OFFICE
17th September 1968



FORMULA I



wherein R' is alkyl straight or branched containing from one to six carbon atoms;

Y is hydrogen, alkyl straight or branched containing from one to fifteen carbon atoms; phenyl; alkoxy straight or branched containing from one to fifteen carbon atoms; hydroxyalkyl containing from one to six carbon atoms, trifluoromethyl; halogen, preferably chloro or

and pharmaceutically acceptable acid addition salts thereof, wherein R is an unbranched alkyl group containing from three to five carbons, or an unbranched alkoxy group containing from three to five carbons.

A novel compound within Formula I o exceptional efficacy is 5(6) - n - Butyl -

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Int. Cl.:—C 07 d 49/38

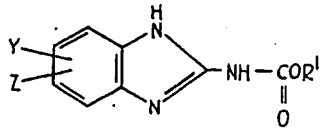
COMPLETE SPECIFICATION

Anthelmintic Compositions containing Benzimidazole Derivatives

We, SMITH KLINE & FRENCH LABORATORIES, of 1500 Spring Garden Street, City of Philadelphia, Commonwealth of Pennsylvania, 19101, United States of America, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to anthelmintic compositions containing esters of benzimidazolyl carbamic acids.

According to the invention, there is provided an anthelmintic composition which comprises an orally ingestible carrier and in association therewith as an anthelmintic agent an ester of benzimidazolyl carbamic acid represented by the general formula:



FORMULA I

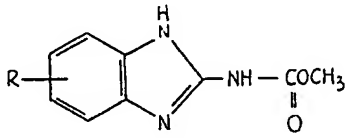
wherein R′ is alkyl straight or branched containing from one to six carbon atoms;

Y is hydrogen, alkyl straight or branched containing from one to fifteen carbon atoms; phenyl; alkoxy straight or branched containing from one to fifteen carbon atoms; hydroxyalkyl containing from one to six carbon atoms, trifluoromethyl; halogen, preferably chloro or bromo; hydroxy; lower alkylthio; alkylamino; dialkylamino; dialkylaminoalkyl; cyano; carboxy; or carbalkoxy containing from two to seven carbon atoms; with the alkyl substituents not specifically defined having from one to seven carbon atoms; and Z is hydrogen, alkyl containing from one to six carbon atoms; or alkoxy containing from one to six carbon atoms; with the limitation that Y and Z are not both hydrogen.

Preferably Y is hydrogen, alkyl, alkoxy, trifluoromethyl, halogen or hydroxy.

The most advantageous compounds are those of Formula I in which R′ is methyl, one of Y and Z is unbranched alkyl containing from one to six carbons, or unbranched alkoxy containing from one to six carbons, and the other is hydrogen.

In accordance with another aspect of the present invention, there are provided novel esters of benzimidazolyl carbamic acid represented by the general formula:



and pharmaceutically acceptable acid addition salts thereof, wherein R is an unbranched alkyl group containing from three to five carbons, or an unbranched alkoxy group containing from three to five carbons.

A novel compound within Formula I of exceptional efficacy is 5(6) - n - Butyl -

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2 - carbomethoxyaminobenzimidazole, which demonstrates excellent activity against the mouse pinworm at 10 mg./kg.; against important sheep nematodes at 5 mg./kg.; and against the migratory stages of *Ascaris suum* in mice at 0.1% of the diet.

Examples of specific compounds falling within Formula I are:

4(7) - Methyl - 2 - carbomethoxyaminobenzimidazole
5(6) - Methyl - 2 - carbomethoxyaminobenzimidazole
5(6) - Methoxy - 2 - carbomethoxyaminobenzimidazole
4(7) - Methoxy - 2 - carbomethoxyaminobenzimidazole
4(7) - Trifluoromethyl - 2 - carbomethoxyaminobenzimidazole
5(6) - Trifluoromethyl - 2 - carbomethoxyaminobenzimidazole
4(7) - Chloro - 2 - carbomethoxyaminobenzimidazole
5(6) - Chloro - 2 - carbomethoxyaminobenzimidazole
5(6) - Hydroxy - 2 - carboethoxyaminobenzimidazole
5(6) - Methylthio - 2 - carboethoxyaminobenzimidazole
5(6) - Methylamino - 2 - carbomethoxyaminobenzimidazole
5(6) - Dimethylamino - 2 - carbomethoxyaminobenzimidazole
5(6) - Dimethylaminomethyl - 2 - carbomethoxyaminobenzimidazole
5(6) - Dimethylaminoethyl - 2 - carbomethoxyaminobenzimidazole
4(7) - Ethyl - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Propyl - 2 - carbomethoxyaminobenzimidazole
4(7) - *n* - Propyl - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Butyl - 2 - carbomethoxyaminobenzimidazole
5(6) - *tert* - Butyl - 2 - carbomethoxyaminobenzimidazole
5(6) - *sec* - Butyl - 2 - carbomethoxyaminobenzimidazole
4(7) - Ethoxy - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Propoxy - 2 - carbomethoxyaminobenzimidazole
4(7) - *n* - Butoxy - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Butoxy - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Pentyl - 2 - carbomethoxyaminobenzimidazole
5,6 - Dimethyl - 2 - carbomethoxyaminobenzimidazole
5(6) - Isobutyl - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Pentoxy - 2 - carbomethoxyaminobenzimidazole
5(6) - Isopentyl - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Hexyl - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Heptyl - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Octyl - 2 - carbomethoxyaminobenzimidazole
5(6) - *n* - Nonyl - 2 - carbomethoxyaminobenzimidazole
2 - Carbomethoxyamino - 5 - (3 - hydroxypropyl) - benzimidazole

It will be readily apparent to one skilled in this art that certain of the substituted 2-aminobenzimidazole compounds (R′ is a branched carbon chain) of this invention may have asymmetric carbon atoms, forming optically active d- and *l*-compounds. The connotation of the general formula presented herein is intended to include the separated d- or *l*-optical isomers, as well as racemic mixtures of these isomers.

If desired, the isomers may be separated for individual use by resolution methods known to the art, such as fractional crystallization of the *l*-tartrate salts of the carbamates. Alternatively, a synthesis starting with an optically active side chain may yield the desired optical isomer.

The compounds of Formula I being weak bases will normally form salts with inorganic and organic acids. Accordingly, the nontoxic salts formed with pharmaceutically acceptable strong inorganic and organic acids may be alternatively employed in the compositions of the invention.

The compounds of Formula I are prepared by reacting cyanamide in a suitable organic solvent, such as pyridine, with the appropriate R′ substituted haloformate to form a cyanocarbamate, followed by the addition of an *o*-phenylenediamine to give the corresponding ester of a benzimidazolyl carbamic acid. Thus, these compounds are readily synthesized by prior art methods.

The haloformate reactant can be a chloroformate or a bromoformate, the chloroformate being preferred for reasons of availability and cost. The choice of the R′ substituted haloformate is of course dependent upon the particular ester product desired.

More specifically, one or two molar equivalents of an *o*-phenylenediamine are added slowly to a solution of the cyanocarbamate and the reaction mixture either heated at steam bath temperature for 1—4 hours or allowed to stand at room temperature for a longer period of time, up to 24 hours. Heating for about 3 hours, following reaction at room temperature for an equal period of time is preferred.

The *o*-phenylenediamine reactant can have substituents on the benzene ring which correspond to Y and Z as defined in Formula I.

The resulting benzimidazoles bear these substituents at the corresponding position of the benzene ring. The nature of the condensation reaction is such that it is generally applicable to *o*-phenylenediamines, regardless of the substituents which may appear on the benzene ring.

An alternative process for making the anthelmintic compounds of this invention starts with an S-lower alkyl pseudothiourea sulfate. This sulfate is treated with one to two equivalents of an R′ substituted haloformate in aqueous solution, and then by condensing with an optionally substituted *o*-phenylenediamine, yields the corresponding benzimidazole-2-carbamic acid ester.

The compounds of Formula I wherein either one or both of Y or Z are alkyl may be prepared starting with the appropriate mono- or di-alkyl benzene. For example, an alkylbenzene is nitrated in the presence of acetic acid to form the *p*-nitro alkyl benzene. This intermediate is reduced with tin chloride to give the corresponding *p*-aminoalkylbenzene, followed by nitration in mineral acid medium with amyl nitrate to give an *o*-nitro-*p*-alkylaniline. This latter intermediate is again reduced with tin chloride to yield a lower alkyl substituted *o*-phenylenediamine. The diamine intermediate is converted by the afore-discussed thiourea sulfate process to the appropriate alkyl substituted benzimidazole-2-carbamic acid ester.

The compounds of Formula I in which Y is dialkylamino and Z is hydrogen, can be prepared starting with dialkylaminobenzene, and following the above-described sequence of steps to yield the dialkylamino substituted benzimidazole-2-carbamic acid ester.

The compounds of Formula I wherein Y is alkylamino and Z is hydrogen, may be prepared starting with 3,4-dinitroaniline. The dinitro compound is treated with, for example, butyryl chloride to yield 1-butyramido-3,4-dinitroaniline, which is reduced with lithium aluminium hydride to yield 1-butylamino-3,4-diaminobenzene. This triaminobenzene is converted to the corresponding benzimidazole-2-carbamic acid ester, by the afore-discussed thiourea method.

The compounds of Formula I wherein Y is alkoxy, and Z is hydrogen, may be prepared starting with 4-hydroxyacetanilide. The anilide is treated with the appropriate alkyl bromide and an alkali metal hydroxide, to yield the corresponding *p*-alkoxyacetanilide, according to the procedure of Buu-Hoi et. al., J. Chem. Soc., 1955, 1573. The substituted compound is nitrated with red fuming nitric acid, while suspended in glacial acetic acid and acetic anhydride at about 0°C. The resulting *o*-nitro-*p*-alkoxyacetanilide is collected, and is recrystallized from methanol. This disubstituted acetanilide is then deacylated by refluxing with an alkali metal hydroxide in ethanol, with the disubstituted aniline being recovered from acidified water. The disubstituted aniline is then hydrogenated at 50—80 psi in benzene, with removal of the solvent by distillation, yielding the corresponding diamine. This diamine intermediate is converted by either of the afore-discussed cyanamide or thiourea sulfate processes to the appropriate lower alkoxy substituted benzimidazole-2-carbamic acid ester.

The compounds of Formula I wherein Y and Z are alkoxy, may be prepared starting with *o*-dihydroxybenzene. The benzene is treated with the appropriate alkyl bromide, and an alkali metal hydroxide in ethanol, to yield the corresponding *o*-dialkoxybenzene. The substituted compound is nitrated with nitric acid while suspended in acetic acid, to yield 1,2 - dialkoxy - 4,5 - dinitro benzene, (*J. Proc. Roy. Soc.*, N. S. Wales, *71*, 103—11, 1938), followed by hydrogenation to give the corresponding substituted diamine. The diamine is converted, as previously described, to a 5,6-dialkoxybenzimidazole-2-carbamic acid ester.

The benzimidazolyl carbamates of Formula I have been found to possess useful anthelmintic properties, that is, broad spectrum activity against parasites of warm blooded animals, including both mature and immature parasitic forms. In particular, these compounds have been found to exhibit high activity against various helmintic infections of the intestinal tract of economically important animals, coupled with low systemic toxicity to the host animal.

Animals of low weight are treated with unit doses ranging no higher than a few milligrams; whereas animals of high body weight, such as ruminants, require proportionately larger unit doses ranging up to several grams. Preferably, a single dose is administered daily for each animal species based on the weight of that species.

The amount of ingredient administered will depend on the weight of the host, but will usually be between about 1 mg./kg. and 500 mg./kg. of body weight daily.

For example, 5(6)-*n*-Butyl-2-carbomethoxyaminobenzimidazole at an oral daily dose of 50 mg./kg. tested in clearing mice of natural pinworm infection, following generally the method of *McCowen et. al.*, reported in the *American Journal of Tropical Medicine, 6*, 894 (1957), gave a 100% result in terms of worms cleared; while a 10 mg./kg. dose gave 93%. Its LD_{50} in mice is in excess of 1 g./kg; and 4 g./kg. in rodents.

In lambs, naturally infested with various gastro-intestinal nematodes, five of the compounds of Formula I were each tested at 5 mg./kg. of body weight (B.W.), in a single dose of 1% concentration in tap water, with the impressive results given in the tabulation below:

Compound	Total Nematodes Mean (3 sheep)	% Reduction
5(6)-*n*-Propyl-2-carbomethoxy-aminobenzimidazole	127	98.8
5(6)-*n*-Butyl-2-carbomethoxy-aminobenzimidazole	187	98.2
5(6)-*n*-Amyl-2-carbomethoxy-aminobenzimidazole	1,298	87.8
5(6)-*n*-Propoxy-2-carbomethoxy-aminobenzimidazole	1,804	83.1
5(6)-*n*-Butoxy-2-carbomethoxy-aminobenzimidazole	240	97.7
Placebo	10,711	—

In lambs, naturally infested with various gastro-intestinal nematodes, three of the compounds of Formula I, (formulated per Example 12) were each tested at the indicated dosages in mg./kg. of body weight (B.W.), in a single dose of 1% concentration in tap water, with the striking results given in the tabulation below:

Compound	Total Nematodes Mean	% Reduction
Placebo	11,649 (3 sheep)	—
Placebo	8,178 (5 sheep)	—
5(6)-*n*-Butyl-2-carbomethoxy-aminobenzimidazole (12.5 mg./kg.)	15 (5 sheep)	99.8
Placebo	7,312 (4 sheep)	—
5(6)-Methoxy-2-carbomethoxy-aminobenzimidazole (15 mg./kg.)	1,676 (4 sheep)	77.0

In practice, a pharmacologically active compound of structural Formula I is usually formulated with a nontoxic carrier therefor to give anthelmintic compositions of this invention. The carrier may be an orally ingestible container for the active ingredient, for example, a hard or soft gelatin capsule; or it may be a pharmaceutically acceptable diluent or excipient of the kind normally used in the production of medicaments, ready for use, for example maize starch, terra alba, lactose, sucrose, calcium phosphate, gelatin, talcum, stearic acid, magnesium stearate, dextrin, agar, pectin or acacia.

Exemplary of liquid carriers are peanut oil, olive oil, sesame oil, and water. Similarly, the carrier or diluent may include a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule, or compounded in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 3 gm. If a liquid carrier is used, the preparation may be in the form of a soft gelatin capsule, placed in an ampule or in liquid suspension.

The compositions are most often made up in a form suitable for internal administration and may therefore take the form of a liquid, for example, an emulsion or a sterile solution or suspension in water, oil, such as arachis oil, or other liquid.

The compositions are advantageously made up in a dosage unit form adapted for the desired mode of administration. Thus, for the preferred oral administration, the dosage unit may take the form of a suspension, tablet,

packaged powder, bolus, or encapsulated powder. The quantity of active ingredient in each dosage unit will be such that one or more units are required for each therapeutic administration.

As previously mentioned, the compounds of formula I have general anthelmintic activity. The daily dose range commonly used is from about 1 mg./kg. to about 500 mg./kg. depending on the species of host and regimen used. One dose per day administration is preferred but up to five of the dosage units described above may be used if desired.

Where tableting is used, the resulting tablets may be coated with methyl methacrylate to form an enteric coating, i.e. a coating which is substantially insoluble in gastric secretion but substantially soluble in intestinal fluids.

It will be appreciated that the active ingredient used in the formulation of tablets may be replaced with other compounds of Formula I having the necessary anthelmintic activity. Furthermore, other materials may be used to form the enteric coating, for example other synthetic plastic materials such as methyl acrylate, cellulose derivatives, hydrogenated caster oil or phthalates.

The compositions thus prepared are administered, usually orally, to an infected host from 1—5 times daily for anthelmintic activity.

The following examples illustrate syntheses which may be employed in preparing the active ingredients and/or formulating the compositions of the invention but are not to be considered as limiting the invention described herebefore.

EXAMPLE 1

Preparation of 5 - *n* - Butyl - 2 - carbomethoxyaminobenzimidazole

Using a 1000 ml. 3-necked, round bottom flask, equipped with a mechanical stirrer, addition funnel, and thermometer, 13.9 g. (0.05 moles) of 2-methyl-2-thiopseudourea sulfate in about 10 ml. of water is stirred in an ice bath. Methyl chloroformate (9.45 g.—0.1 moles) is added at one time. The mixture is stirred at 0°C., for ten minutes, then a total of 19 ml. of 25% sodium hydroxide is added over ten minutes while maintaining the temperature below 20°C.

At this point the pH is about 8 and remains there after 5 minutes of stirring. Ten ml. of acetic acid is added, making the pH about 5 and keeping the temperature about 20°C.

A solution of 4-*n*-butyl-*o*-phenylenediamine in ethanol, prepared from 11.9 g. (0.05 mole) of the hydrochloride, is added to the reaction mixture.

The addition funnel is replaced by a condenser, attached to three traps for methyl mercaptan, one empty and two with 10% aqueous NaOH. Heat is applied very slowly to the stirred mixture, with gas evolving constantly. As the temperature rises slowly, ethanol is added, to control foaming. The total reflux time is about ¾ of an hour. The reaction is cooled to room temperature and left over the week-end.

A light tan solid is collected, washed with water, then suspended in 50% aqueous ethanol, and recollected. The solid is dried on a porous plate in an oven.

The product is recrystallized from 1200 to 1400 ml. of 30-ethanol plus 150 ml. of water, and is left in a refrigerator overnight. The product is collected and washed twice with 20% aqueous ethanol.

The product is then recrystallized again from 20% aqueous ethanol. It is dried *in vacuo* over P_2O_5, to give pure product, m.p. 225—7°C. (d).

The structure is confirmed by elemental analysis and spectral data.

EXAMPLE 2

Preparation of 2 - Carbomethoxyamino - 5 - *n* - Propylbenzimidazole

The starting material 4-*n*-propylnitrobenzene is converted to 4-*n*-propylaniline by treatment with stannous chloride dihydrate in alcoholic medium. 2-Nitro-4-propylaniline is prepared from the previous compound by treatment with *tert*-butanol and amyl nitrate. The preceding 2-nitro compound is reduced with stannous chloride in alcoholic medium to yield 4-*n*-propyl-o-phenylenediamine.

Following the procedure detailed in Example 1, 8.2 g. of 4-*n*-propyl-*o*-phenylenediamine, 7.8 g. of methyl chloroformate, and 15.2 g. of 2-methyl-2-thiopseudourea sulfate in aqueous medium are reacted to give 10.25 g. of crude product, m.p. 234—235°C. Two recrystallizations from 85% aqueous ethanol gives off-white crystals, which are dried *in vacuo* over P_2O_5, to give 7.7 g. of pure product, m.p. 239—240.5°C., (d), whose structure was confirmed by elemental analysis and spectral data.

EXAMPLE 3

Preparation of 5 - *n* - Amyl - 2 - Carbomethoxyaminobenzimidazole

Following the procedure detailed in Example 2, 4-*n*-amyl-*o*-phenylenediamine was prepared starting with 4-*n*-amylaniline, by nitration and reduction to the diamine.

2-Methyl-2-thiopseudourea sulfate (12.0 g.) is reacted with 6.15 g. of methyl chloroformate, and 7.7 g. of 4-*n*-amyl-*o*-phenylenediamine to give 8.5 g. of crude product, m.p. 215—218°C., (d).

Two recrystallizations from 85% aqueous ethanol, followed by drying *in vacuo* over P_2O_5, gave 7.0 g. of a pure product, m.p. 228—230°C., (d) whose structure was confirmed by elemental analysis and spectral data.

EXAMPLE 4

Preparation of 5 - *n* - Propoxy - 2 - Carbomethoxyaminobenzimidazole

4-*n*-Propoxy-1,2-diaminobenzene is prepared as follows: 4-hydroxyacetanilide (151 g.), 750 ml. of ethanol, and 56 g. of potassium hydroxide are mixed together, after which *n*-propylbromide (125 g.) is added all at once, while the reaction mixture is maintained under a nitrogen atmosphere. The mixture is refluxed for three hours, then cooled to 0°C., whereupon 1 liter of water is added and a cream colored crude product is collected and air dried. After drying *in vacuo* at room temperature a dry 4-propoxy compound, m.p. 118—120°C. remains.

4-Propoxy-2-nitroacetanilide is prepared from the above intermediate (46.3 g.) by mixing and warming on a steam bath with 60 ml. of glacial acetic, 20 ml. acetic anhydride, and 50 ml. of water. Stirring is continued at room temperature until crystals begin to form at about 40°C. Then 20 ml. of concentrated nitric acid are added and the temperature rises being held at about 60—65°C. for ten minutes with an ice bath. It is cooled slowly over a 15 minute period to 25°C. with a yellow product precipitation at about 35°C., which is collected, and dried *in vacuo* at room temperature. 4-Propoxy-2-nitroacetanilide, m.p. 88—91°C., is recrystallized from 50% ethanol.

The acetanilide is deacylated to form the corresponding aniline with Claisen's alkali (Org. Syn. Col., Vol. III, pages 663). The reaction is carried out under a nitrogen atmosphere while being refluxed for 20 minutes. At the end of the reflux period the dark solution which forms is cooled, and a red solid product (4-propoxy-2-nitroaniline) is collected, which is dried *in vacuo* at room temperature over night.

4-Propoxy-*n*-phenylenediamine is prepared by reduction of the above nitroaniline with stannous chloride in HCl solution. The nitroaniline is added portionwise, maintaining the temperature at 100—105°C. for 30 minutes. The reaction solution is diluted with 200 ml. of water, and cooled to 25°C., then made strongly basic with 40% sodium hydroxide. A brown solid forms which is cooled, and placed *in vacuo* at room temperature over night. The intermediate is redissolved in ether, with the resulting organic layer being separated and dried over sodium sulfate. After filtering, the ether solvent is stripped, yielding the desired diamine.

Using the procedure detailed in Example 1, the desired benzimidazole product is prepared by treating 55.7 g. of 2-methyl-2-thiopseudourea sulfate with 37.8 g. of methyl chloroformate, and 33.2 g. of the previously prepared substituted-*o*-diaminobenzene to give a crude product. Recrystallization from dimethylsulfoxide, then washing with ethanol gave pure product, which is dried *in vacuo* over P_2O_5 yielding 11.85 g., m.p. 230—230.5°C., whose structure was confirmed by elemental analysis and spectral data.

EXAMPLE 5

Preparation of 5 - *n* - Butoxy - 2 - Carbomethoxyaminobenzimidazole

Following the procedure detailed in the preceding Example, 4-*n*-butoxy-*o*-phenylenediamine is prepared starting with *p*-hydroxyacetanilide by alkylation, nitration, deacylation, and reduction to the 4-*n*-butoxy-*o*-phenylenediamine. 2-Methyl-2-thiopseudourea sulfate (55.7 g.), is reacted with 37.8 g. of methyl chloroformate, and 36.0 g. of the above diamine, to give the crude product. The crude product is dissolved in dimethylsulfoxide at 100°C., filtered, and allowed to cool to room temperature. The product is collected, washed with ethanol, and air dried to yield pure product (24.7 g.), m.p. 224—225°C., whose structure was confirmed by elemental analysis and spectral data.

EXAMPLE 6

Preparation of 2 - Carbomethoxyamino - 5 - *n* - Hexylbenzimidazole

Following the procedure described in Example 4, 4-*n*-hexyl-*o*-phenylenediamine was prepared starting with *n*-hexylbenzene, firstly by sequential nitration, then reduction to yield 4-*n*-hexylaniline. Slow addition to the substituted aniline of acetic anhydride, followed by 70% HNO_3, yielded 2-nitro-4-*n*-hexylacetanilide.

The separated solid anilide (110 g.) is placed in 250 cc. concentrated hydrochloric acid, followed by the addition of 480 cc. of ethanol, then by treatment with 480 cc. stannous chloride dihydrate in 604 cc. of concentrated HCl. The reaction mixture is neutralized, and extracted with ether, yielding the desired 4-*n*-hexyl-*o*-phenylenediamine.

To an aqueous solution of 2-methyl-2-thiopseudourea sulfate (36.3 g.) is added 18.7 g. of methyl chloroformate, followed by addition of 26.1 g. of the previously prepared diamine in aqueous ethanol solution, yielding 22.0 g. of crude product.

Two recrystallizations from 85% aqueous ethanol yield purified product of light brown platelets (12.5 g.), m.p. 221.5—223.0°C., (d), whose structure was confirmed by elemental analysis and spectral data.

EXAMPLE 7

Preparation of 5,6 - Dimethyl - 2 - carbomethoxyaminobenzimidazole

Using a 1-liter 3-necked, round-bottomed flask, equipped with mechanical stirrer, addition funnel, and thermometer, 20.4 g. (0.0735 moles) of 2-methyl-2-thiopseudourea sulfate in 70 ml. of water, is stirred and maintained at 0°C. Methyl chloroformate (13.9 g.—.147 moles) is added all at once, followed by the addition of about 40 ml. of 25% aqueous sodium hydroxide, which is added drop-wise

keeping the temperature about 15°C. and the pH about 6.

At 15°C., 18 ml. glacial acetic acid is added dropwise over about 5 minutes reducing the pH to between 5 and 6.

Ten g. (.0735 mole) of comminuted 4,5-dimethyl-*o*-phenylenediamine is added all at once to the reaction mixture, followed by 20 ml. of water.

A condenser replaces the funnel, and the gas outlet on the condenser is attached to a series of three traps, two traps containing about 10% sodium hydroxide. Heat is applied very slowly, and as the temperature rises gas evolves. Ethanol is added to maintain stirrability. After one-half hour at 95°C., the reaction mixture is further diluted with water and cooled. The pasty mixture is filtered and washed with water, followed by washing with an ethanol: water mixture. It is collected, and dried overnight on a porous plate.

The product (13.3 g.) is recrystallized from 350 ml. dimethylsulfoxide plus 320 ml. of ethanol, and left in a refrigerator overnight. Crystals are collected, washed with cold ethanol, and air-dried. The solid product is boiled twice with 250 ml. of water, collected, air-dried, and dried at 25°C. *in vacuo* over P_2O_5, to give pure product, having a m.p. of 295—305°C. (d).

The structure is confirmed by elemental analysis and spectral data.

Example 8

Preparation of 5,6 - Dibutoxy - 2 - Carbomethoxyaminobenzimidazole

Catechol (55 g.) and 150 g. of *n*-butyl bromide were brought to a reflux in 250 ml. of absolute ethanol. Potassium hydroxide (60 g.) of water is added slowly, to minimize the violent reaction which occurs, with an ice bath being employed to maintain temperature control. The reaction solution is refluxed under nitrogen atmosphere for two hours; then another 50 g. of butyl bromide and 20 g. of KOH in 15 ml. of water is added, and the refluxing continued for another two hours. The solution is cooled, 500 ml. of water is added to dissolve the salt, and the aqueous solution is extracted with ether. The ether extract is washed, dried over sodium sulfate, filtered, and removed, leaving a yellow liquid (1,2-dibutoxybenzene) which is distilled *in vacuo* b.p. 113—116°C.

To a solution of 1,2-dibutoxybenzene (50 g.) in 100 ml. of glacial acetic acid is added with stirring 30 ml. of concentrated nitric acid in 50 ml. of glacial acetic acid. The temperature is maintained at 65°C., after which the solution is stirred for 30 minutes; it is then poured into 40 ml. of water where upon a solid forms, that is collected after cooling. A pale yellow solid (1,2-dibutoxy-4-nitrobenzene) is recrystallized from 30% ethanol having a m.p. 53—54°C.

1,2-Dibutoxy-4-nitrobenzene (10 g.) is treated with 70 ml. of concentrated nitric acid, with stirring, while warming slowly on a steam bath. An oil forms which begins to solidify, with heating being continued for about 30 minutes. The solution is diluted with 70 ml. of water and cooled. A yellow solid (1,2-dibutoxy-4,5-dinitrobenzene), is collected, water washed, and air-dried, m.p. 120—122°C.

The dinitrobenzene compound (1.65 g.) is hydrogenated catalytically (5% Palladium on carbon—0.16 g.) while dispersed in ethanol (175 ml.) and ethyl acetate (40 ml.). Room temperature was maintained and pressure at 50 psi in a Parr Shaker for 3½ hours. Two equivalents of ethereal HCl are added after the catalyst. Catalyst was removed by filtering through a Celite mat, and the solvent stripped. The word "Celite" is a Trade Mark. A dark solid product (2 g. of 4,5-dibutoxy-*o*-phenylenediamine) is collected under a nitrogen atmosphere.

With the procedure detailed in Example 1, 1.33 g. of the above diamine, 0.95 g. methyl chloroformate, and 0.7 g. of 2-methyl-2-thiopseudourea sulfate in aqueous medium, are reacted to give 1.1 g. of crude product.

Two recrystallizations from dimethylformamide give a pure product, which is dried *in vacuo* over P_2O_5, m.p. 290.0°C. (d), whose structure is confirmed by elemental analysis and spectral data.

Example 9

Preparation of 2 - Carbomethoxyamino - 5 - chlorobenzimidazole

Cyanamide (18.6 g.—0.444 moles), dried *in vacuo* over P_2O_5, is dissolved in 225 ml. dry pyridine and is chilled in an ice bath. The solution is stirred continuously as 34.2 ml. (42 g. = 0.444 moles) of methyl chloroformate is added fairly slowly, keeping the temperature below 26°C. The solution is stirred in an ice bath for 10 minutes after the addition is completed, and then at room temperature for 1 hour. 4-Chloro-*o*-phenylenediamine (63.6 g.—0.444 moles) is added. The dark red solution is stirred at room temperature for ½ hour, and is heated on the steam bath for 5 hours.

The pyridine is evaporated with stirring at 50°C., and the resultant slurry of black oil and solid is mixed with 300 ml. ethanol, warmed slightly, and stirred until all of the black oily liquid dissolves. Only crystalline material is left undissolved. Water (100 ml.) is added and the pyridine is filtered off, washed with ethanol and dried overnight on a porous plate. Crude yield is 13.3 g. (0.59 moles).

The product is suspended in 400 ml. of 1:1 of ethanol: water, then 100 ml. of 2.5 NaOH is added. The solution turns black, and almost all of the solid dissolves. The insoluble material is filtered off and the pH

of the solution is adjusted to 7.5 using glacial acetic acid. A light grey solid appears. It is collected, washed with 50% aqueous ethanol, and dried on porous plate. (Yield = 10.2 g.)

The product is further purified by dissolving in dimethylsulfoxide at 100°C., filtering the dark solution and adding an equal volume of hot methanol. The final precipitate is light tan colored and decomposes with melting at 295—300°C. In order to get rid of residual dimethylsulfoxide, the solid product is stirred with boiling water twice, and then filtered off. It is dried at 25°C. *in vacuo* over P_2O_5.

The structure is confirmed by elemental analyses and spectral data.

EXAMPLE 10

Preparation of Substituted 2 - Carbalkoxyaminobenzimidazoles

When the following substituted *o*-phenylenediamines are substituted for the *o*-phenylenediamine in the procedure of Example 1, the corresponding listed products are obtained:

Starting Material	Product
4-Chloro-*o*-phenylenediamine	2-Carbomethoxyamino-5(6)-chlorobenzimidazole, m.p. 295—300° C.
4-N,N-Dimethylamino-*o*-phenylenediamine	5(6)-N,N-Dimethylamino-2-carbomethoxyaminobenzimidazole, m.p. 236—237.5° C.
3-*n*-Propyl-*o*-phenylenediamine	2-Carbomethoxyamino-4-*n*-propylbenzimidazole, m.p. 147—148° C.
4-*n*-Amyloxy-*o*-phenylenediamine	5(6)-Amyloxy-2-carbomethoxyaminobenzimidazole, m.p. 211—213° C.
4-Methyl-*o*-phenylenediamine	2-Carbomethoxyamino-5(6)-methylbenzimidazole, m.p. 297—303° C. (d)
4-Ethoxy-*o*-phenylenediamine	2-Carbomethoxyamino-5(6)-ethoxybenzimidazole, m.p. 223—225° C.
4-Ethyl-*o*-phenylenediamine	5-Ethyl-2-carbomethoxyaminobenzimidazole, m.p. 237—238.5° C.
4-Isobutyl-*o*-phenylenediamine	5-Isobutyl-2-carbomethoxyaminobenzimidazole, m.p. 285° C. (d)
4-*tert*-Butyl-*o*-phenylenediamine	5-*tert*-Butyl-2-carbomethoxyaminobenzimidazole, m.p. 221—223° C. (d)
4-Isopropoxy-*o*-phenylenediamine	2-Carbomethoxyamino-5(6)-isopropoxybenzimidazole, m.p. 213—215° C.
4-Phenyl-*o*-phenylenediamine	2-Carbomethoxyamino-5(6)-phenylbenzimidazole, m.p. 265° C. (d)

EXAMPLE 11

Typical Cattle Bolus Containing an Anthelmintic Described Herein

5(6)-*n*-Propyl-2-carbomethoxyamino-benzimidazole	2.0 grams
Calcium phosphate	2.5 grams
Maize starch	0.54 grams
Talcum	0.14 grams
Gum arabic	0.15 grams
Magnesium stearate	0.05 grams

The calcium phosphate and the anthelmintic compound are thoroughly mixed, and the mixture reduced to a particle size finer than 60 mesh. About one-half of the starch is added, as an aqueous paste, and the resulting mixture granulated. The granules are passed through a No. 10 mesh (U.S.S.S.) screen and dried at 110—130°F. for about 8 hours. The dried materials are then passed through a No. 16 mesh (U.S.S.S.) screen. The guar gum and the balance of the starch are added and the mixture thoroughly blended. Finally, the remainder of the ingredients are added and the entire mass thoroughly mixed and compressed into a bolus. The magnesium stearate, talcum and gum acacia are of a particle size to pass a No. 10 mesh (U.S.S.S.) screen.

EXAMPLE 12

Typical Sheep Drench Containing an Anthelmintic Described Herein

	Parts by Weight
5(6)-*n*-Amyl-2-carbomethoxyamino-benzimidazole	60
Terra Alba English	35.5
Tragacanth, U.S.P.	3.0
Sodium Lauryl Sulfate	1.5
Water	q.s.

EXAMPLE 13

Novel Sheep Drench Containing an Anthelmintic Carbamate

	Parts by Weight
5(6)-*n*-Butyl-2-carbomethoxyamino-benzimidazole	80.0
Atmos 300 [a]	5.0
Starch, U.S.P.	12.0
Tragacanth, U.S.P.	3.0
Water	q.s.

[a] Mono and diglycerides of fat-forming fatty acids supplied by Atlas Chemical. The word "Atmos" is a Trade Mark.

The above solid components are thoroughly mixed, giving a water dispersible powder. This powder can be directly admixed with water in concentrations on the order of 5 g. of powder to 5 cc. of water.

EXAMPLE 14

Novel Sheep Drench Containing an Anthelmintic Carbamate

	Parts by Weight
5(6)-*n*-Butoxy-2-carbomethoxyamino-benzimidazole	60
Terra Alba English	16
Methyl cellulose	1
Polyethylene glycol (Methocel 4000)	20
Antifoam AF [a]	3

[a] Silicone emulsion supplied by Dow Chemical Co.

The above ingredients are suspended, one part powdered mixture to four parts water, and spray dried as is well known in the art.

EXAMPLE 15

Novel Anthelmintic Suspension for Human Administration

	% w/v
*5-*n*-Butyl-2-carbomethoxyamino-benzimidazole	5.000
Methocel, 15 cps. (Methylcellulose, USP)	1.500
Duponol C (Sodium Lauryl Sulfate, USP)	0.100
Ethylparaben	0.060
Propylparaben, USP	0.013
Glycerin, USP	10.000
Citric Acid, Reagent grade	0.100
Sodium Citrate, USP	0.180
Sucrose, USP	20.000
Antifoam AF (Dow Corning)	0.100
Purified water, USP q.s. ad	100.000

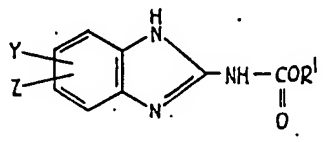
Susceptible helminths in monkeys include *Oesphagostomum* spp., *Protospirura* spp., *Trichostrongylus* spp., *Strongyloides* spp., *Physalaptera* spp., and *Trichuris* spp.

* Passed through Trost Mill twice.

The compounds of the invention also possess antiviral activity. In particular, the 5 - *n* - Butyl - 2 - Carbomethoxyaminobenzimidazole compound is active in mice at 5 to 100 milligrams per kilograms against vaccinia infections and shows *in vitro* activity against vaccinia virus, and influenza A; WSN strain and NWS strain.

WHAT WE CLAIM IS:—

1. A composition having anthelmintic activity in animals, which comprises an orally ingestible carrier and in association therewith as an anthelmintic agent a compound represented by the general formula:



or a pharmaceutically acceptable acid addition salt thereof wherein:

R′ is alkyl straight or branched containing one to six carbon atoms;

Y is hydrogen, alkyl straight or branched containing from one to fifteen carbon atoms, alkoxy straight or branched containing from one to fifteen carbon atoms, phenyl, hydroxyalkyl containing from one to six carbon atoms, trifluoromethyl, halogen, hydroxy, lower alkylthio, alkylamino, dialkylaminoalkyl, dialkylamino, cyano, carboxy, or carbalkoxy containing from two to seven carbon atoms, with the alkyl substituents not specifically defined having one to seven carbon atoms; and

Z is hydrogen, alkyl containing from one to six carbon atoms, or alkoxy containing from one to six carbon atoms, with the limitation that Y and Z are not both hydrogen.

2. A composition as claimed in Claim 1, wherein Y is hydrogen, alkyl, alkoxy, trifluoromethyl, halogen or hydroxy.

3. A composition as claimed in Claim 1, wherein one of Y and Z is unbranched alkyl containing from one to six carbons or unbranched alkoxy containing from one to six carbons, and the other is hydrogen, and R′ is methyl.

4. A composition as claimed in Claim 1, wherein the anthelmintic agent is 5(6) - *n* - propoxy - 2 - carbomethoxyaminobenzimidazole.

5. A composition as claimed in Claim 1, wherein the amthelmintic agent is 5(6) - *n* - butyl - 2 - carbomethoxyaminobenzimidazole.

6. A composition as claimed in Claim 1,

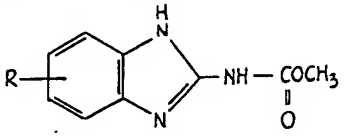
wherein the anthelmintic agent is 5(6) - *n* - butoxy - 2 - carbomethoxyaminobenzimidazole.

7. A composition as claimed in Claim 1, wherein the anthelmintic agent is 5(6) - *n* - propyl - 2 - carbomethoxyaminobenzimidazole.

8. A composition as claimed in Claim 1, wherein the anthelmintic agent is 5(6) - *n* - amyl - 2 - carbomethoxyaminobenzimidazole.

9. An anthelmintic composition substantially as described in any one of the foregoing Examples 11 to 15.

10. Esters of benzimidazolyl carbamic acid represented by the general formula:



and pharmaceutically acceptable acid addition salts thereof, wherein R is an unbranched alkyl group containing from three to five carbons, or an unbranched alkoxy group containing from three to five carbons.

11. 5(6) - *n* - Butyl - 2 - carbomethoxyaminobenzimidazole.

12. 5(6) - *n* - Butoxy - 2 - carbomethoxyaminobenzimidazole.

13. 5(6) - *n* - Propyl - 2 - carbomethoxyaminobenzimidazole.

14. 5(6) - *n* - Propoxy - 2 - carbomethoxyaminobenzimidazole.

15. 5(6) - *n* - Amyl - 2 - carbomethoxyaminobenzimidazole.

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